

REMARKS

Claims 7, 12, 13, 15-21, 43, 73, 75, 80, 81 and 83 have been cancelled, Claims 3-6, 10, 11, 72, 76, 78, 79 and 82 have been amended, and Claims 86-152 have been added. No new matter has been added. Claims 3-6, 10, 11, 42, 72, 74, 76-79, 82, 84-152 are pending.

Support for the recitation “agent” in amended Claims 3-6, 10, 11, 72, 76, 78, 79 and 82 is found, for example, in the specification at page 7, lines 14-20 and page 20, line 4 *et seq.*

Support for the recitation “a soluble polypeptide comprising the extracellular domain of a receptor of the Ephrin family ligand” in amended Claims 11 and 79 is found, for example, in the specification at page 28, lines 12-19.

Support for new Claims 86 and 89 is found, for example, in the specification at page 8, lines 9-12, page 17, lines 26-33 and page 28, lines 12-24.

Support for new Claims 87, 88, 90, 91 is found, for example, in the specification at page 30, lines 15-30.

Support for new Claims 92 and 93 is found, for example, in the specification at page 29, line 25 to page 30, line 2.

Support for new Claim 94 is found, for example, in the specification at page 30, lines 3-30 and in Claims 3 and 7 as originally filed.

Support for the recitation “agent” in new Claims 94, 96, 97, 99-101, 104, 107, 108, 112, 116, 117, 121, 126, 128-130, 133-142, 147 and 148 is found, for example, in the specification at page 7, lines 14-20 and page 20, line 4 *et seq.*

Support for new Claims 95-97, 103 and 106 is found, for example, in the specification at page 5, lines 14-18, page 30, lines 4-14 and in Claim 4 as originally filed.

Support for new Claims 98-100 is found, for example, in the specification at page 5, lines 14-18, page 30, lines 4-14 and in Claim 5 as originally filed.

Support for new Claims 101, 102, 104 and 105 is found, for example, in the specification at page 28, lines 9-12 and page 30, lines 8-10.

Support for new Claims 107, 108, 112, 116, 117, 121, 128 and 130 is found, for example, in the specification at page 30, lines 3-14.

Support for new Claims 109-111, 113-115, 118-120 and 122-124 is found, for example, in the specification at page 30, lines 15-30.

Support for new Claims 125 is found, for example, in the specification at page 28, lines 12-24.

Support for new Claims 126, 127 and 129 is found, for example, in the specification at page 29, line 29 to page 30, line 2.

Support for new Claims 131, 132, 151 and 152 is found, for example, in the specification at page 3, lines 19-28, page 5, lines 20-33 and page 15, line 19 *et seq.*

Support for new Claim 133 is found, for example, in the specification at page 27, lines 15 *et seq.* and in Claim 8, 10 and 12 as originally filed.

Support for new Claims 134, 140 and 142 is found, for example, in the specification at page 19, lines 17-22 and page 27, lines 15-19.

Support for new Claims 135 and 136 is found, for example, in the specification at page 29, line 29 to page 30, line 2 and in Claims 13 and 14 as originally filed.

Support for new Claim 137 is found, for example, in the specification at page 28, lines 28-31.

Support for new Claim 138 is found, for example, in the specification at page 17, lines 26-33 and page 28, lines 1-5.

Support for new Claim 139 is found, for example, in the specification at page 28, line 33 to page 29, line 4.

Support for new Claim 141 is found, for example, in the specification at page 17, lines 1-6, page 22, lines 30-34, page 24, lines 18-20 and page 28, line 33 to page 29, line 4.

Support for new Claims 143-145 is found, for example, in the specification at page 28, lines 9-12 and page 29, lines 7-19.

Support for new Claim 146 is found, for example, in the specification at page 28, lines 12-19.

Support for new Claims 147 and 148 is found, for example, at page 28, lines 9-12, at page 29, line 29 to page 30, line 2, and in Claims 13 and 14 as originally filed.

Support for new Claims 149 and 150 for example, in the specification at page 24, line 14 *et seq.* and at page 26, line 25 to page 27, line 1.

The amendments to the claims are supported by the application as filed. Therefore, this Amendment adds no new matter.

Additional remarks addressing the issues and rejections presented in the Office Action are set forth below with reference to the numbered paragraphs in the Office Action.

Paragraph 6. Provisional Double Patenting Rejection of Claims 3, 5, 7-10, 12, 42, 43, 72, 80 and 85 Under 35 U.S.C. § 101

The Examiner has maintained her provisional rejection of Claims 3, 5, 7-10, 12, 42, 43 and 72 under 35 U.S.C. § 101 as claiming the same invention as that of Claims 3, 5, 7-10, 12, 42, 43 and 72 respectively, of co-pending Application No. 09/687,652. The Examiner has also provisionally rejected Claims 80 and 85 under 35 U.S.C. § 101 as claiming the same invention as that of Claims 44 and 43 respectively, of co-pending Application No. 09/687,652.

As noted by the Examiner in the previous Office Action (Paper No. 18), the rejection is a provisional rejection because the claims of co-pending U.S. Patent Application No. 09/687,652 have not been patented. Applicants will address the rejection of Claims 3, 5, 7-10, 12, 42, 43, 72, 80 and 85 in the subject application if the claims of co-pending U.S. Patent Application No. 09/687,652 are allowed or patented before the claims of the subject application.

If this provisional rejection is the only rejection remaining after entry and consideration of this Amendment, Applicants request that the Examiner withdraw the rejection and permit the subject application to issue as a patent, in accordance with U.S. Patent Office procedure (see, M.P.E.P. § 804(I)(B)).

Paragraph 7. Provisional Rejection of Claims 73-75, 76 and 79 Under the Judicially Created Doctrine of Obviousness-type Double Patenting

The Examiner has maintained her provisional rejection of Claims 73-75 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 71, 72 and 8 respectively, of co-pending Application No. 09/687,652. The Examiner has also provisionally rejected Claims 76 and 79 under the judicially created doctrine of obviousness-

type double patenting as being unpatentable over Claims 3 and 10 respectively, of co-pending Application No. 09/687,652. As indicated in the Examiner's previous Office Action (Paper No. 18), it is the Examiner's opinion that although the conflicting claims are not identical, they are not patentably distinct from each other because they are overlapping in scope.

If this provisional rejection is the only rejection remaining after entry and consideration of this Amendment, Applicants request that the Examiner withdraw the rejection and permit the subject application to issue as a patent, in accordance with U.S. Patent Office procedure (see, M.P.E.P. § 804(I)(B)). Applicants will consider filing a terminal disclaimer or otherwise address this rejection in co-pending U.S. Application No. 09/687,652.

Paragraph 8. Rejection of Claims 3, 5, 42, 73, 76, 77, 81 and 85 Under 35 U.S.C. § 112, first paragraph

Claims 3, 5, 42, 73, 76, 77, 81 and 85 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement commensurate with the scope of the claims. According to the Examiner, while one of skill in the art could, given the teachings of the specification, identify artery-specific ephrin family ligands and vein-specific eph family receptors, the skilled artisan could not predictably use them as broadly claimed. In the Examiner's opinion, the claims require not only that the molecules be expressed specifically, but that they also be involved in angiogenesis and Applicants have not provided any guidance to indicate that any eph or ephrin family members other than ephrinB2 and ephB4 would affect angiogenesis (Office Action, page 3, lines 9-13).

The Examiner further states that differential expression, if observed, would not be predictive of such a function and that the eph/ephrin families are involved in many different processes and their precise functions are not clear (Office Action, page 3, lines 13-15). The Examiner concludes that without further guidance indicating that differentially expressed eph/ephrin pairs could, if identified, be predictably used as claimed, it would require undue experimentation for the skilled artisan to use the invention as broadly claimed in Claims 3, 5, 42, 73, 76, 77, 81 and 85 (Office Action, page 3, line 20 to page 4, line 2).

Claims 73 and 81 have been cancelled thereby obviating the rejection to these claims. Applicants respectfully disagree with the Examiner's rejection of Claims 3, 5, 42, 76, 77 and 85

under 35 U.S.C. § 112, first paragraph, as lacking enablement commensurate with the scope of the claims. The standard for determining whether the specification meets the enablement requirement is whether a person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Id.* at 737.

In the present case, Applicants have disclosed methods of determining tissue distribution of identified genes using, for example, *in situ* hybridization (Specification, page 34, line 25 *et seq.*). Applicants have further identified and described structural elements of the Ephrin family of ligands and Eph family of receptors (Specification, page 9, line 22 *et seq.*). For example, the specification teaches:

The ephrins (ligands) are of two structural types, which can be further subdivided on the basis of sequence relationships and, functionally, on the basis of the preferential binding they exhibit for two corresponding receptor subgroups. Structurally, there are two types of ephrins: those which are membrane-anchored by a glycerophosphatidylinositol (GPI) linkage and those anchored through a transmembrane domain. Conventionally, the ligands are divided into the Ephrin-A subclass, which are GPI-linked proteins which bind preferentially to EphA receptors and the ephrinB subclass, which are transmembrane proteins which generally bind preferentially to EphB receptors.

Specification, page 9, lines 22-33. Applicants' specification further teaches that the Eph family of receptors are protein tyrosine kinases which are divided into two subgroups based of their ability to bind preferentially to ephrinA proteins or ephrinB proteins and provides a table of representative Eph receptors and their respective Ephrin ligands (Specification, page 10, line 1 to page 11, line 18).

It is clear that one of skill in the art, with Applicants' teachings of the differential vascular expression of EphrinB2 and EphB4, would be able to identify other genes (e.g., other Ephrin ligands and/or other Eph receptors) which are differentially expressed in vascular tissue using methods taught in Applicants' specification (e.g., *in situ* hybridization, differential screening) and/or other art-standard methods (e.g., Northern blot hybridization, immunohistochemistry, RT-PCR analysis). It is also clear that one of skill in the art, using Applicants' teachings of the generation of *ephrinB2* transgenic mice and/or other art-standard methods, could test whether

such identified genes have a role in angiogenesis and/or give rise to vascular defects when mutated.

For example, using RT-PCR analysis, *in situ* hybridization analysis and whole-mount immunohistochemistry with labeled Ephrin ligands and labeled Eph receptors, Adams *et al.* examined expression of various Ephrin ligands and Eph receptors in vascular tissue (Adams *et al.*, page 296, column 2, section entitled “Coexpression of multiple ephrins and Eph receptors in yolk sac and embryonic blood vessels” and Figs. 1 and 2, Reference AY2 in the Third Supplemental Information Disclosure Statement being filed concurrently herewith). Using these art-standard techniques, Adams *et al.* were able to demonstrate that the Eph receptor, EphB3, did not exhibit homogeneous vascular expression but rather exhibited prominent expression on all major veins and specific expression on aortic arches, but no expression on other arteries (Adams *et al.*, page 297, column 2, first paragraph and Fig. 2E). Using Applicants’ teachings, Adams *et al.* were able to independently confirm the mRNA vascular expression patterns of the Ephrin ligands and Eph receptors that they examined by detecting receptor protein through ephrin-B2-AP (ephrinB2-alkaline phosphatase) staining of veins and aortic arches (Adams *et al.*, page 297, column 2, first paragraph). Adams *et al.* also demonstrated co-expression of ephrinB1 and ephrinB2 on arteries, co-expression of eprinB1, ephrinB2 and EphB3 on aortic arches, and co-expression of ephrinB1, EphB3 and EphB4 on veins (Adams *et al.*, page 296, column 2, section entitled “Coexpression of multiple ephrins and Eph receptors in yolk sac and embryonic blood vessels” and Figs. 1 and 2).

Based on their expression results and using methods disclosed in Applicants’ specification and/or art-standard methods, Adams *et al.* were able to demonstrate that while *ephB2* and *ephB3* homozygous mice did not display any vascular defects, *ephB2/ephB3* double-mutant mice displayed vascular defects and defective angiogenesis with about 30% penetrance (Adams *et al.*, page 298, column 2 to page 300, column 1 and Figures 4 and 5). The *ephB2* (also known as *nuk*), *ephB3* (also known as *sek4*) and *ephB2/ephB3* mutant mice used in the studies performed by Adams *et al.* were generated using methods described in Applicants’ specification and/or art-standard methods (Adams *et al.*, page 304, column 1, Materials and Methods, section entitled “Targeting vectors and generation of mutant mice”). Thus, similar to the methods used by Applicants to generate *ephrinB2* mutant mice (see Specification, page 33, line 5 *et seq.* and

page 35, line 1 *et seq.*), the *ephB2* mutant mice (*nuk^{lacZ}*) used in the studies performed by Adams *et al.* were generated by targeting and replacing the endogenous *ephB2* gene with a mutant *ephB2* gene comprising the extracellular, transmembrane and juxtamembrane domains of *ephB2* linked in frame to β-galactosidase (Henkemeyer *et al.*, page 44, column 2, section entitled “*Nuk Gene targeting*” and page 36, Figure 1, Reference AZ2 in the Third Supplemental Information Disclosure Statement being filed concurrently herewith). Similarly, the *ephB3* mutant mice (*sek4*-/-) used in the studies were generated by targeting and replacing the endogenous *ephB3* gene with a mutant *ephB3* gene lacking most of the exons of the kinase domain and comprising a PGK promoter-driven neomycin cassette (Orioli *et al.*, page 6036, column 1, section entitled “*Inactivation of the sek4 gene*” and page 6037, Figure 1, Reference AR3 in the Third Supplemental Information Disclosure Statement being filed concurrently herewith). It should be noted that the mutant *ephB2* (i.e., *nuk*) and *ephB3* (i.e., *sek4*) mice used in these studies were generated in 1996, prior to the filing date of the subject application (see, for example, Henkemeyer *et al.* and Orioli *et al.*).

Thus, using methods disclosed in Applicants’ specification and/or art-standard methods, Adams *et al.* were able to demonstrate that the EphB3 receptor did not exhibit homogeneous vascular expression and that *ephB2/ephB3* double-mutant mice displayed vascular defects and defective angiogenesis (Adams *et al.*, whole document). These results clearly demonstrate that it would not require undue experimentation for a person of ordinary skill in the art, with the teachings of Applicants’ specification in hand, to practice the invention as claimed by Applicants in Claims 3, 5, 42, 76, 77 and 85. Applicants’ specification, combined with the general knowledge of the art, therefore provides an enabling disclosure to practice the claimed invention.

Moreover, Applicants’ invention is a pioneering invention which provides motivation for others to examine the expression and vascular effects that other Ephrin ligands and/or Eph receptors possess using methods disclosed in Applicants’ specification and/or art-standard methods (see for example, Adams *et al.*, whole document). Restriction of the claimed invention to a particular Ephrin ligand (e.g., EphrinB2) and/or particular Eph receptor (e.g., EphB4) would unduly limit Applicants’ invention and invite those of skill in the art to easily design around Applicant’s invention. The court has clearly stated that “[d]epriving inventors of claims which adequately protect them and limiting them to claims which practically invite appropriation of the

invention while avoiding infringement inevitably has the effect of suppressing disclosure.” In re Angstadt and Griffin, 190 USPQ 214, 219 (CCPA 1976). Therefore, reconsideration and withdrawal of the rejection of Claims 3, 5, 42, 76, 77 and 85 are respectfully requested.

Third Supplemental Information Disclosure Statement

A Third Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the Third Supplemental Information Disclosure Statement is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTSClaim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Claims 7, 12, 13, 15-21, 43, 73, 75, 80, 81 and 83 have been cancelled and Claims 86-152 have been added.

3. (Twice Amended) A method for altering angiogenesis in a mammal, comprising administering to the mammal, in a therapeutically effective quantity, [a drug] an agent which alters the specific binding of an Ephrin family ligand with an Eph family receptor.
4. (Twice Amended) The method of Claim 3 wherein angiogenesis is inhibited and the [drug] agent interferes with the specific binding of the Ephrin family ligand with the Eph family receptor.
5. (Three Times Amended) The method of Claim 3 wherein angiogenesis is enhanced and the [drug] agent enhances specific binding of the Ephrin family ligand with the Eph family receptor.
6. (Twice Amended) The method of Claim 3 wherein the [drug] agent is an antagonist of the Ephrin family ligand or an antagonist of the Eph family receptor.
10. (Twice Amended) A method for selectively delivering [a drug] an agent to arteries in a mammal, comprising administering to the mammal a complex comprising:
 - a) the [drug] agent; and
 - b) a component which binds an Ephrin family ligand,under conditions appropriate for the component of (b) to bind the Ephrin family ligand, whereby the [drug] agent is delivered to arteries.

11. (Twice Amended) The method of Claim 10 wherein the [drug] agent is an anti-angiogenic [drug] agent and the component of (b) is selected from the group consisting of an antibody specific for the Ephrin family ligand [or] and a soluble polypeptide comprising the extracellular domain of a receptor of the Ephrin family ligand.
72. (Twice Amended) The method of Claim 10 wherein the [drug] agent is an angiogenic [drug] agent.
76. (Amended) The method of Claim 3 wherein the [drug] agent is an agonist of the Ephrin family ligand or an agonist of the Eph family receptor.
78. (Amended) The method of Claim 10 wherein the [drug] agent is an anti-angiogenic [drug] agent.
79. (Amended) The method of Claim 10 wherein the [drug] agent is an angiogenic [drug] agent and the component of (b) is selected from the group consisting of an antibody specific for the Ephrin family ligand [or] and a soluble polypeptide comprising the extracellular domain of a receptor of the Ephrin family ligand.
82. (Amended) The method of Claim 10 wherein the [drug] agent is an anti-plaque agent.